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A randomized, controlled trial of a multi-modal exercise intervention in Huntington's disease

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ABSTRACT

Introduction: This study aimed to evaluate the feasibility and benefit of a structured exercise intervention in people with Huntington's Disease (HD).

Methods: This study was conducted at 6 sites, and participants were randomized into either exercise or control (usual care) groups, and were assessed at baseline, 13 and 26 weeks. The intervention was a 12 week, three times per week progressive exercise program, including aerobic (stationary cycling) and upper and lower body strengthening exercise with tapered 1:1 support for 20 of 36 sessions.

Results: 314 adults were assessed for eligibility: 248 did not meet inclusion criteria, 34 declined, and 32 were recruited and randomized. Three individuals in the intervention group were withdrawn within the first month due to concomitant medical conditions, resulting in 14 participants in intervention and 15 in control groups. There were two AEs in the intervention group, both related to previous medical conditions, and there were two SAEs, both in the control group. The intervention group had better fitness (predicted VO₂ max difference: 492.3 ml min⁻¹, 95% CI: [97.1, 887.6]), lower UHDRS mMS (difference 2.9 points, 95% [−5.42, −0.32]) and lower weight at Week 13 (difference 2.25 kg, 95% CI: [−4.47, −0.03]).

Conclusion: This study demonstrates that a short-term exercise intervention is safe and feasible. Individuals with HD may benefit from structured exercise, and intensity, monitoring and support may be key factors in optimizing response. Larger scale trials are now required to fully elucidate the extended clinical potential of exercise in HD.

Trial registration: Current Controlled Trials ISRCTN11392629.

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1. Introduction

Aerobic and multi-modal exercise interventions are well known for their effect on cardiorespiratory fitness, muscle strength, depression and cognition [1], and in recent years, benefits of exercise and physical activity have been studied in Huntington

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disease (HD) animal models [2] and people with HD [3–6]. Furthermore, longer term multidisciplinary rehabilitation has resulted in improvements in gait, balance and quality of life [7,8], and evidence suggests it may impact cognitive function [9]. However, clear benefit as a result of participating in a shorter-term exercise program incorporating targeted aerobic and strength training has yet to be established.

A variety of challenges are associated with exercise interventions in people with complex neurodegenerative diseases such as HD, not least that associated with cognitive and motor signs of the disease. In a recent study, a home-based exercise intervention was well received by participants; however, carer support was needed to facilitate and at times supervise the exercise program [3]. Results from a gym-based program suggest that while it was safe and feasible for individuals to engage in an aerobic exercise program, overall intensity of the intervention may not have been sufficient to achieve a training effect [4]. Information obtained from process interviews also suggested that some participants found the gym environment intimidating. In order to develop a successful exercise intervention, acceptable to a wide number of people with HD, it is critical to include personal preferences of exercise environment to facilitate uptake and adherence.

Complex physical and cognitive impairments in HD can impact on a person's ability to initiate and adhere to an exercise program [10]. Ensuring sufficient intensity of exercise to achieve an aerobic effect is a further challenge. Thus a supported, structured, mixed delivery approach may facilitate a wider range of people with HD to engage in exercise. Here we present results from a randomized controlled trial of an exercise program delivered with tapered professional support. This study was designed to evaluate a more intensive, progressive exercise program than has been previously studied in this population. The specific objectives were to identify whether a 3-month, three times per week exercise program in people with HD was: 1) safe, 2) feasible in terms of adherence and retention, 3) improved physical fitness, and 4) improved functioning in other domains, such as motor and cognitive function.

2. Methods

2.1. Study design

This was a single-blind, multi-site randomized controlled trial of an exercise intervention compared to usual care. Assessments were taken at baseline and 13 weeks. Follow up phone calls were made at 26 weeks to assess health status and physical activity. Fig. 1 illustrates the CONSORT flowchart.

2.2. Site and participant selection

The trial was carried out at six HD specialist clinics that were ENROLL-HD/Registry (13/WA/0192), sites: Cardiff, UK; Birmingham, UK; Oxford, UK; Leiden, Netherlands; Münster, Germany; and Oslo, Norway. ENROLL-HD is a worldwide observational study of Huntington's disease families, and provides a platform for clinical studies to facilitate recruitment into clinical trials. Exclusion and inclusion criteria are shown in Table 1.

2.3. Recruitment

The recruitment period was March 2014 to January 2015 with a target of 42 participants. Patients receiving routine HD clinical care or attending an ENROLL-HD assessment were given trial information. An invitation letter and information sheet was sent to ENROLL-HD patients who were potentially eligible but not due to visit clinic imminently; those participants subsequently attended

an ENROLL-HD appointment and were reviewed by the site Principal Investigator (PI). All participants gave written informed consent. Site PIs were responsible for ensuring that each participant was capable of giving informed consent.

2.4. Screening

Each site kept a screening log, which recorded details of number of people approached about the trial and eligibility.

2.5. Blinding

Data collection was conducted by blinded assessors. Site coordinators requested participants not disclose their allocation to the assessors. Incidents of unblinding were recorded.

2.6. Randomization

The trial coordinator performed randomization centrally for each participant during their baseline assessment; group assignment was conveyed to respective site coordinators by phone, who then informed the participant privately following completion of baseline assessment. Randomization ratio of intervention to control arm was 1:1. A minimization procedure [11] was used to achieve balance between groups; variables used for minimization were site, age, gender, and Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS TMS) [12].

2.7. Intervention

The intervention group participated in a 12-week exercise program; control group was asked to continue as usual. The intervention consisted of a 50-min structured aerobic, strengthening and stretching routine, and could take place either in a hospital-based gym, or participant's home with exercise equipment provided by the researchers. Physical therapists or certified fitness professionals (referred to as trainers henceforth) delivered the intervention, and monitored prescribed exercise dose, progression and safety. Trainers provided support in a tapered process for 20/36 sessions: for weeks 1–2, trainers supervised 3/3 sessions; for weeks 3–6, 2/3 sessions were supervised with 1 independent session; for weeks 7–12, 1/3 sessions were supervised.

Sessions followed a set program including a 5-min warm up and up to 25 min on the bike within an aerobic zone. Intensity of warm-up was at 50–60% age predicted maximum heart rate (APMHR, defined as 220-age) and aerobic zone was in a range of 65–85% APMHR. Trainers progressed participants by initially working to achieve the full 30 min of training time and then increasing intensity within the training zone. During the last 3 min, intensity was tapered to the lower end of training zone. Following the aerobic exercise was 10–15 min of strengthening, consisting of lower extremity and core activities, ending with 5 min of stretching (see Appendix 1).

In supported sessions, trainer's recorded detailed resistance, speed of pedalling, heart rate (HR) and perceived exertion at 5-min intervals for aerobic training on the bike, and sets, repetitions and weights for strengthening exercises. Participants were provided with exercise diaries for independent sessions.

Participants assigned to the control group were instructed to continue as normal. Following completion of the study, control group participants were offered gym membership for 12 weeks or a home exercise bike, including two trainer visits.

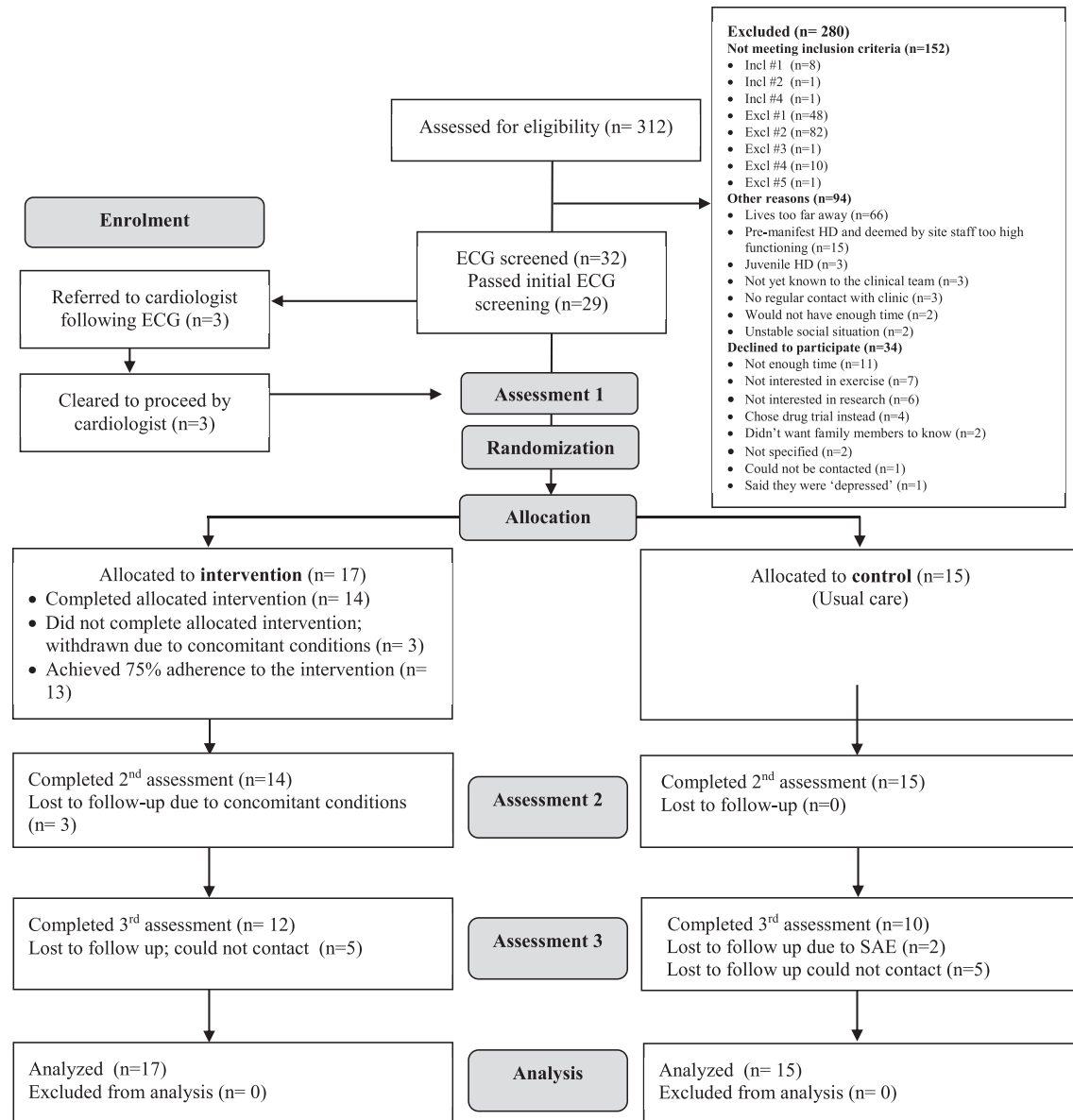


Fig. 1. ExeRT-HD CONSORT Flow chart.

Table 1
Participant inclusion/exclusion criteria.

Inclusion criteria	Exclusion criteria
1) genetically confirmed diagnosis of HD	1) any physical or psychiatric condition that would prohibit the participant from completing the intervention or the full battery of assessments
2) above the age of 18 years	2) inability to independently use the exercise bike
3) stable medication regime for four weeks prior to initiation of trial, and anticipated to be able to maintain a stable regime for the course of trial	3) unable to understand or communicate in spoken English (UK sites only)
	4) currently involved in any intervention trial or within four weeks of completing an intervention trial
	5) current, regular participation in a structured exercise program five times per week or more

HD = Huntington's disease.

2.8. Safety for exercise

Participants were screened for risk factors for exercise [13], and completed the Physical Activity Readiness Questionnaire (PAR-Q) [14] and a resting electrocardiogram (ECG) to ensure safety to

initiate an exercise program. If abnormal results were found participants were referred to their primary physician or cardiologist, depending on the site, for further evaluation before being allowed to enrol in the trial.

2.9. Baseline assessment

We collected demographic data of age and gender, and height and weight were measured. Medication was recorded at baseline and any medication changes at Week 13 were noted. Medications were coded according to classification and indication.

2.10. Outcomes

Outcomes of safety, feasibility, and effectiveness were assessed. Safety was assessed by review of weekly health and falls diaries, which included information on falls history, medication changes, healthcare service use and hospital admissions (classified as adverse events (AEs)). Diaries were given to all participants at baseline assessment and were returned at Week 13.

The primary feasibility objective was evaluation of recruitment, retention and adherence rates. Recruitment was assessed using site recruitment logs. Retention rate was measured as percentage of individuals who completed the intervention. Adherence rates were defined as percentage of intervention sessions completed. Successful intervention adherence was pre-defined as at least 75% of supervised sessions (15/20 sessions), and 75% of unsupervised sessions (12/16 sessions), completed with average HR over session duration within the aerobic zone.²

The primary efficacy outcome in terms of short-term benefit was physical fitness measured using a predicted VO₂ max equation [15], by stepwise incremental exercise test (Appendix 2).³ Expired air and capillary blood samples⁴ were collected at two sites during the exercise test. Expired air measures provided information about gas exchange during exercise, which was used to validate the predicted test equation [15].

Secondary outcome measures included measures of motor function, ambulation and cognition (Appendix 3).

2.11. Training and site monitoring

We conducted a one-day training for assessors and trainers, which was videotaped for future viewing. Additional on-site training was conducted.⁵ Assessors conducting UHDRS TMS and mMS were required to have Motor Rating Certification [16]. Monitoring occurred face-to-face or via remote video on at least two occasions per site. Trainers maintained detailed session notes for each training session, which were reviewed by the PI during the trial to assure intervention fidelity.

2.12. Sample size

We planned to recruit 42 participants to allow us to estimate any feasibility proportion to within plus or minus 15.1% points. While demonstrating efficacy was not an aim of the study, with 34 participants in total (17 per group, 20% attrition) we could detect a standardised difference of 1.0 at the final measurement point with a power of 80%.

² Acceptability of the intervention and further analysis of intervention fidelity and progression was assessed via structured questionnaires with research participants and trainers on completion of the intervention and will be reported elsewhere; manuscript in preparation.

³ Cardiff and Oxford sites utilized Lode Excalibur Sport bike, Gronigen, Netherlands; all other sites utilized a Monarch 874E bike, Monark Exercise AB, Vansbro, Sweden).

⁴ Full results from the expired air and blood samples will be reported elsewhere; manuscript in preparation.

⁵ Training for the Norway site, which was added mid-way through the trial, was conducted via remote video-conferencing.

2.13. Statistical analysis

Descriptive data includes evaluation of eligibility, recruitment, retention and adherence rates with 95% confidence intervals. Predicted VO₂ max was compared to actual VO₂ max (baseline) on data from two sites using Pearson correlation coefficients. Graphical illustrations were used to check distributions of outcome data. Primary and secondary analyses compared outcome measures between intervention and control groups, using Analysis of Covariance (ANCOVA) controlling for age, UHDRS TMS, gender and baseline measure on the outcome of interest. A pre-defined statistical analysis plan was followed. All analyses were conducted on an intention-to-treat basis; primary analysis used complete case data set.

2.14. Ethics

The trial was approved by Wales Research Ethics Committee 2 (Wales REC 2; 13/WA/0315).

3. Results

3.1. Recruitment and randomization

Three hundred and fourteen adults were assessed for eligibility over 11 months, and 32 were recruited and randomized (50%, 95% CI [38.1,61.9]) (see Fig. 1). Recruitment was monitored throughout the trial; two sites had low recruitment secondary to staffing issues, so another site was added. Seventeen participants were randomized to intervention; eight exercised at home and nine in a hospital/research laboratory. Twenty-six of the 32 participants were taking one or more medications at the time of baseline assessment. Table 2 provides baseline data and medication use for both groups.

3.2. Adverse events (AE)

Two AEs occurred in the intervention group. Symptoms of concomitant conditions were aggravated during the intervention (recurrence of back pain in one participant and Wolf Parkinson White syndrome in another). The participants were subsequently withdrawn. Two serious adverse events (SAEs) occurred in the control group. One SAE was attempted suicide, which occurred within one week after Week 13 Assessment, and was classified as possibly related. While it is impossible to make a direct correlation between the assessment and attempted suicide, the worst-case classification was adopted. The participant was hospitalized and returned home with community psychiatric team support. The other SAE was a suicide and classified as unlikely to be related.⁶

3.3. Retention

Three individuals (intervention group) were withdrawn within the first month due to concomitant medical conditions (Fig. 1), resulting in 14 participants in the intervention and 15 in the control group for final analysis (retention rate of 90.6%, 95% CI [73.4, 97.5]). All assessors remained blinded throughout the study.

⁶ The site PI confirmed that there were no suicidal plans at the time of the participant's most recent clinical visit. The SAE occurred 3 months following the second assessment and 2 months following the last study contact date when the trainer delivered the control intervention program between Assessment 2 and 3.

Table 2

Baseline Characteristics and Medication use for all participants. Mean (SD) [Range] Scores are reported for age, Total functional capacity, Total Motor score, and Symbol Digit Modality.

Variable	Control group (n = 15)	Intervention group (n = 17)
Gender (men:women)	7:8	9:8
Age (y)	51(17) [19–76]	53 (11) [22–69]
Total functional capacity score (TFC)	9 (3) [3–13]	8 (3) [2–13]
UHDRS Total Motor Score (TMS)	32 (14) [12–54]	39 (22) [4–85]
UHDRS Symbol Digit Modality Test	28 (10) [14–45]	23 (9) [6–44]
Cognitive assessment (SDMT)		
Medications	Antichoreic (n = 4) Antidepressant (n = 8) Antihypertensive (n = 1) Analgesic (n = 4) Other (n = 8)	Antichoreic (n = 4) Antidepressant (n = 11) Antihypertensive (n = 4) Analgesic (n = 0) Other (n = 8)
Medication changes	n = 3 Addition of anti-choreic (n = 1); Addition of diabetes management medication (n = 1); Course of antibiotics (n = 1)	n = 2 Increase in anti-hypertensive (n = 1); Decrease in anti-depressant (n = 1)

3.4. Intervention adherence

Thirteen of the 14 participants who completed the trial completed >75% of the required sessions (92.9%, 95% CI [64.2,99.6]); one participant completed 61% of sessions secondary to illness. For the aerobic exercise, 10/13 achieved average target HR within aerobic zone (65–85% APMHR) for at least 75% of the sessions; 3/13 were able to achieve HR at 60% APMHR. UHDRS TFC scores for these participants were 2, 6, and 7 and UHDRS TMS were 85, 65 and 66 respectively, indicative of middle-late stages of the disease.

3.5. Falls

Twenty-one out of 32 participants completed the health and falls diaries. Mean (median) number of falls in control group was 1.12(1) (n = 8; 1 excluded) and 0.83(0) (n = 12) in intervention group. Diaries for one participant were excluded due to inaccurate completion.

3.6. Outcomes

Predicted VO₂ max for each participant at two sites was compared to actual VO₂ max obtained from expired air (r = 0.88, n = 15⁷).

The intervention group had better fitness as measured by predicted VO₂ max (Table 3) (difference: 492.3 ml min⁻¹, 95% CI: [97.1,887.6]). There was also improvement on UHDRS mMS (intervention arm 2.9 points lower, 95% [-5.42, -0.32]). Weight was different between groups at follow up (intervention arm 2.25 kg lighter 95% CI: [-4.47, -0.03]). There were no differences between groups on other outcome measures.

At Week 26 phone call, nine control participants and nine intervention participants provided EQ-5D scores. EQ-5D mean (SD) scores in control and intervention arms were 0.78(0.14) and 0.80(0.21) respectively. Eight control participants and nine intervention participants provided IPAQ scores. Mean (SD) IPAQ scores in control and intervention arms were 1753(1802) and 988(890) respectively.

4. Discussion

Here we report data from a short-term, multi-modal exercise program in people with HD with tapered support. The intervention was safe and feasible, and evaluation of exploratory outcomes revealed significant improvements in fitness and motor function. We demonstrated that people with HD could exercise safely in an aerobic zone and conduct progressive strengthening exercises, despite the presence of sometimes advanced motor impairments. Importantly, individuals in the intervention group did not have a greater incidence of falls or AEs compared to control participants.

Individuals in the intervention group demonstrated lower weight at Week 13 compared to control group. While in the general population weight loss after exercise is generally considered a positive outcome, in this population it is not necessarily desirable. Weight loss is common in HD and has been shown to be correlated with CAG repeat [17]. Previous studies in animal models of HD have also shown a propensity towards weight loss following exercise [2]. The role of nutrition to supplement potential weight loss from increased physical activity will be an important component of future trials and should likely include analysis of body composition.

This study initially aimed to recruit 42 participants, which was not achieved within a 10 month time period; this was primarily due to site staffing issues. In addition, we had a large number of participants who did not meet inclusion/exclusion criteria. While many of these individuals had psychiatric or behavioural problems, these criteria conceivably excluded potential participants who may benefit most from exercise, such as those with anxiety or depression. Despite this, our study included individuals with a wide range of motor and functional capacity.

Physical limitations and inability to use the exercise bike were also primary reasons for exclusion; this was likely representative of individuals in the mid-late stages of the disease, who may be more appropriate for other types of rehabilitation intervention (e.g. task specific training [18]). In addition approximately 20% of participants lived too far away to participate, either for the participant or trainer to travel for training sessions. As HD is a relatively rare disease, future studies should include strategies to promote remote training and monitoring, or local professionals to support exercise programs.

This intervention incorporated a tapered support program, providing 1:1 instruction for the first weeks that decreased over 12 weeks. Trainers served two important purposes: to monitor that the program was being conducted as intended, and to provide support and encouragement to facilitate adherence. The support structure appears to have been effective, in that 13/14 participants adhered to the program, with only one participant having lower

⁷ Data from 2 participants at the Cardiff site is missing from this analysis; one due to difficulty with a participant using the equipment, one secondary to equipment malfunction.

Table 3
Unadjusted Descriptive Statistics Split by Group for all Outcome Measures at baseline and 13 weeks, along with adjusted treatment effect estimates from a complete case ANCOVA Analysis.

Construct	Outcome measure	Baseline				Week 13				Adjusted estimate of visit 2 and effect sizes from ANCOVA ^a	p-value	
		Control		Intervention		Control		Intervention				
		Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n			
									Treatment effect estimate (95% CI)	Effect size		
Fitness	Predicted VO2 Max (ml.min-1)	1767.39 (755.28)	15	1585 (546.14)	15	1812.49 (672.5)	13	2045.77 (687.66)	14	492.32 (97.08, 887.56)	0.73	0.02
Motor function	UHDRS modified Motor Score (mMS) [21]	15 (7)	15	18 (7)	17	14 (7)	15	16 (7)	14	-2.87 (-5.42, -0.32)	-0.43	0.03
	15 rep chair stand time (sec) ^a [22]	47.1 (19.9)	15	47 (26.6)	17	42.3 (17.3)	15	47.6 (21.4)	14	-5.57 (-23.99, 17.32)	N/A	0.59
	Three minute walk (m) [23]	213.7 (72.6)	15	225.8 (73.8)	17	220.1 (71.1)	15	218.5 (50.9)	14	4.68 (-20.38, 29.74)	0.08	0.70
	Finger Tapping score (no.taps in 10 s) ^a [24]	33.6 (12.4)	15	27.5 (13.1)	16	34.4 (13.4)	15	30 (11.3)	14	12.69 (-9.22, 39.88)	N/A	0.26
Physical Activity	IPAQ MET-Minutes [25]	1335.2 (1002.7)	15	1249.7 (1054.4)	17	1347.7 (1839.7)	15	3104.4 (3836.7)	14	1288.67 (-459.05, 3036.4)	0.42	0.14
Dual-tasking	Simple dual task walk time (sec) [26]	14.04 (7.02)	15	12.85 (4.11)	17	13.08 (6.38)	15	12.54 (3.61)	14	0.29 (-2.79, 3.37)	0.06	0.85
	Complex dual task walk time (sec) [26]	22.93 (19.5)	15	16.41 (4.99)	17	17.84 (10.06)	15	15.48 (5.03)	14	1.42 (-2.71, 5.56)	0.18	0.48
Cognition	Symbol Digit Modalities Test (no. correct) [27]	28 (10)	15	23 (9)	17	29 (9)	15	23 (12)	14	0.09 (-3.04, 3.22)	0.01	0.95
	Category Verbal Fluency (no. correct) [12]	17 (5)	15	13 (6)	17	17 (5)	15	12 (5)	14	-1.13 (-4.83, 2.57)	-0.2	0.53
	Stroop colour naming (no. correct) [12]	47 (12)	15	41 (16)	17	48 (13)	15	39 (14)	14	-4.27 (-10.16, 1.63)	-0.31	0.15
	Word reading (no correct) [12]	64 (15)	15	57 (21)	17	65 (22)	15	53 (19)	14	-5.39 (-17.55, 6.76)	-0.26	0.36
	Interference (no correct) [12]	27 (8)	15	23 (9)	17	27 (9)	15	23 (9)	14	0.71 (-3.79, 5.21)	0.08	0.74
	Trailmaking A time (sec) ^a [27]	54.9 (22.3)	15	82.1 (59.2)	17	51.7 (18.7)	15	91.6 (61.7)	14	8.54 (-12.39, 34.45)	N/A	0.43
Depression	Trailmaking B time (sec) [27]	133 (69)	15	153.1 (65.7)	15	145.2 (71.9)	15	171.5 (79.4)	14	-1.76 (-40.86, 37.33)	-0.02	0.92
	Hospital Anxiety and Depression Scale ^a [28]	11 (9)	15	9 (9)	17	11 (9)	15	7 (6)	14	-20.61 (-59.55, 54.9)	N/A	0.50
Global Health	EQ-5D-3L [29]	0.74 (0.17)	15	0.77 (0.19)	17	0.75 (0.19)	15	0.81 (14)	14	0.055 (-0.097, 0.207)	0.34	0.42
Weight	Weight (kg)	76.5 (18.3)	15	79.9 (16.5)	17	77.2 (18.3)	15	80 (16.3)	14	-2.25 (-4.47, -0.03)	-0.13	0.047

^a Log transformed hence % difference between arms (with 95% CI) rather than adjusted treatment effect.

than 75% adherence secondary to illness. Follow up phone calls at Week 26 suggested that while general health outcome remained relatively unchanged, participants in the intervention group appeared to return to low levels of physical activity after the support structure was removed.

Three participants in this study were unable to consistently achieve 65% APMHR while exercising on the bike. This was likely due to motor and coordination impairments, which may make it difficult for people with HD to maintain the speed necessary to achieve a higher HR. Despite this, an overall effect of improving fitness was seen, which indicates that in this population 60% APMHR may be adequate to achieve a training effect (e.g. change in VO₂ max).

Positive results in terms of safety, feasibility and outcomes suggest that a larger scale, confirmatory trial of exercise intervention in people with HD is now warranted. This study has indicated that predicted VO₂ max is sensitive to change in this population, and thus demonstrates the construct validity of VO₂ max as an outcome measure for an exercise intervention in this population. For future studies, based on the observed effect size in predicted VO₂ max of 0.73 we would require 41 participants per group (for analysis) in order to have 90% power to identify this effect as statistically significant at the 5% level using a two-sided comparison of means.

4.1. Limitations and future directions

As a feasibility study, and one of the first to systematically evaluate a multi-modal exercise intervention in HD, we considered it important to not add complexity through the introduction of an active comparator, which should be included in future studies.

These may include interventions that focus on physical activity education as well as different modes and intensities of exercise. Future studies should also consider additional measures of functional abilities, disease-specific quality of life and measures of muscle strength.

While this study demonstrated changes in fitness and motor function, there was not carry over to walking ability or sit to stand, or to cognitive function. Extending the intervention to longer durations may be important to evaluate the potential for exercise to have effects on cognition and other functional abilities [19,20]. Furthermore, exercise may be most feasible and have the potential for disease modification for individuals in the pre-manifest or prodromal stages of HD, and consideration of early intervention is necessary. Finally, studies are needed to fully understand the mechanistic underpinnings by which exercise can exert its effects across all stages of the disease.

The findings in this study are generalizable to a relatively limited number of individuals with HD, who are mobile and have limited behavioural or psychiatric issues. We recognize that our exclusion criteria potentially limited a large number of individuals with HD who may have most benefited from the intervention, however we believed it important to set these criteria as a minimum requirement for ethical and scientific reasons and to establish feasibility in a subgroup most likely to complete and potentially benefit from the intervention.

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Conflict of interest

No authors declare a conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2016.06.023>.

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